chloride (DANSC), tetramethylrhodamine isothiocyanate (TRITC), lissamine, rhodamine 8200 and sulphonyl chloride (RB 200 SC).

Remarks

The Office Action, dated September 13, 2000, has been carefully considered. The claims have been amended to more clearly set forth the Applicants' contribution to the art and do not introduce new matter into the disclosure of the invention. The basis for the amendments to the claims can be found on pages 10-21 and further on pages 28-31 of the Specification. It is believed that no additional fee is required as the number of independent and dependent claims is the same as originally filed. The amendments are those that the Examiner has indicated would address the issues raised by the application. Furthermore, in light of the amendments, the Examiner has indicated that the previous New Matter and section 112, first paragraph rejections will be withdrawn.

The Examiner has rejected claims 1-23 and 25-42 under 35 U.S.C. 112, first paragraph contending that these claims, while being enabled for in vivo targeting of secreted analytes in the blood from the circulatory system does not reasonably provide enablement for in vivo targeting of other analytes secreted in other body fluids such as in cases of infection in synovial fluid or cerebrospinal fluid. Specifically the Examiner contends that the specification does not enable any person skilled in the art to which it pertains to use the invention commensurate in scope with these claims.

Claim 1 has now been amended to provide the additional limitation that the target analyte is a peptide or protein hormone. Furthermore, claim 1 has been amended to provide that the method is specifically directed to targeting analytes in vivo in the blood. Antecedent basis for these changes can be found on page 14, lines 4-11, page 15, lines 6-10, page 17, lines 9-16 and page 28, lines 9-13.

Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 1-23 and 25-42 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the application regards as the invention. The claims have now been amended herein to address the issues raised by the Examiner as discussed in the earlier telephonic interview.

Specifically, the Examiner contends that claim 1, step (h) is confusing because it appears to claim a correlation step between the amount of target analyte that is determined and the amount of targeting moiety:target analyte conjugate bound to the capture moiety that is detected but fails to specifically indicate the relationship between these two. Claim 1, step (h) has now been amended to recite a step of determining the amount of target analyte in the sample correlating to the amount of conjugate bound to the capture moiety as described in step (g).

The Examiner contends that claim 6 is indefinite in reciting acronyms. Claim 6 has now been amended to fully define the abbreviations with the claim.

The Examiner contends that claim 7 is vague, indefinite and indeterminate in scope in reciting "extracellular fluid" because it is unclear what is encompassed by the term as recited in the claim. Claim 7 has now been amended in view of the narrowing of scope of claim 1 to recite blood as the bodily fluid selected from the group consisting of blood serum and plasma.

The Examiner contends that with regard to claim 8, the phrase "fragments thereof" renders the claim indefinite because the claim includes elements not actually disclosed. Claim 8 has now been amended to delete reference to such fragments.

The Examiner contends that claims 20, 22 and 23 are confusing in reciting a "second targeting moiety" which appears to encompass the capture moiety in claim 1. Claim 20 has now been amended to further define that the second targeting moiety is

recognized by the capture moiety thereby eliminating the references in claims 20, 22 and 23.

The Examiner contends that claim 26 lacks antecedent support in reciting "the molecule capable of binding". Claim 26 has now been amended to reference the second targeting moiety.

The Examiner contends that claim 37 is indeterminate in scope for reciting inconsistent language and lacks antecedent support in reciting "paratopic molecules". Claims 37, 38 and 39 have now been amended to delete references to paratopic molecules and instead reference the targeting moieties. Based on the foregoing amendments and remarks, it is submitted that the 35 U.S.C. 112 rejections have been overcome and it is respectfully requested that they be withdrawn.

Rejection Under 35 U.S.C. 103

The Examiner has rejected claims 1 - 23 and 25 - 42 under 35 U.S.C. 103(a) as being unpatentable over Tamarkin, et al (U.S. 5,587,294) and Pouletty, et al (U.S. 5,612,034) in view of David, et al (U.S. 4,486,530). Applicants maintain the arguments of record and respectfully traverse this rejection.

The present invention as defined by the amended claim 1 relates to a method of measuring basal as well as stimulated analyte production in vivo. The references cited by the Examiner do not provide the necessary specific motivation much less a reasonable expectation of the success in solving the issues of the present invention. Applicants submit herewith a Declaration from the Applicants demonstrating that one of ordinary skill in the art of immunology and medical science would not deduce the present invention upon reading the references cited by the Examiner either alone or in combination.

While Tamarkin discloses a competitive solid phase immunoassay for measuring the concentration of proteins, Tamarkin fails to teach injecting an excess of

targeting moiety to a human in order to form a targeting analyte complex. The complex formed increases the life span of the target analyte in vivo without interfering with any in vivo processes that depend on the macromolecule of interest. The accumulation of the analyte of interest allows one to measure the amount of macromolecule secreted over an amount of time and not just the amount at any instant. The ability to detect and measure macromolecules normally not present in measurable quantities is novel. Furthermore, the present invention allows a human or animal subject to be injected more than one or to do several different macromolecules at once without affecting the results.

Furthermore, Tamarkin fails to use immunometric sandwich assays using monoclonal antibodies in measuring the concentration of macromolecules in a sample. Pouletty discloses injecting a target moiety or a binding entity into the bloodstream of a mammalian host for binding the target analytes essentially binding an analyte with a targeting moiety to allow for capture of the target analyte. Again there is no suggestion that this method could be used to measure an analyte production over time or that an excess of targeting moiety would need to be used in order to measure the total quantity.

Pouletty *et al.* teaches only that one can increase the in vivo biological half-life of a compound that normally has a short in vivo half-life by injecting it into an animal so that it binds covalently to a molecule that naturally has a long in vivo half-life. Pouletty does not suggest that increasing the half-life would provide the results of the present invention by using an excess of a neutralizing binding molecule that prevents catabolism.

David discloses a two-site or sandwich immunometric assay for determining the concentration of target analyte in fluids using monoclonal antibodies, but merely provides known method for immunometric assays and does not provide any motivation or suggestion to combine with the other teachings to reach the present invention.

In summary, one skilled in the art would find nothing in Tamarkin and Pouletty in view of David either alone or in combination that would teach or suggest the present invention or a motivation for making the present invention. Furthermore, there is no motivation to combine the references in such a way as to arrive at the claimed invention. Therefore, the present invention is not obvious under 35 U.S.C. 103 and accordingly, an obviousness rejection under this section is improper and the Applicants respectfully request reconsider and withdrawal of this rejection.

In view of the above, it is respectfully submitted that the claims as amended and presented before the Examiner are in condition for allowance. Accordingly, reconsideration and withdrawal of the rejections are requested and allowance of claims 1, 4-23 and 25-42 is solicited.

Respectfully submitted,

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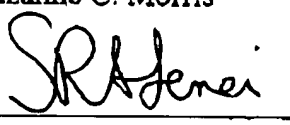
By 

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